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Supplementary Information

Acid-cleavable polymers for simultaneous fast and slow release of functional molecules

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S1. Experimental Section

S1.1. Materials

n-Butyl methacrylate (BMA, >99%, TCI chemical) was purified by vacuum distillation before using. Acryloyl chloride and methacryloyl chloride were synthesized according to a reported method by distillation a mixture of acrylic acid or methacrylic acid and benzoyl chloride.[S1] 8-quinolinyl 3-((2-hydroxyethyl)thio)propanoate (QAOH) was produced according to a previous report.[S2] Nicotinoyl chloride hydrochloride was prepared according to the reported method by reaction with oxalyl chloride.[S3] 4-(vinyloxy)butyl methacrylate (VBMA) and 4-(1-(benzotriazole-*N*-yl) ethoxy)butyl methacrylate (BEBMA) were prepared from 1,4-butanediol and vinyl ether with methacryloyl chloride by a previously reported method.[S4] Dichloromethane (DCM, 99.9%, Carlo Erba), chloroform (98%, Carlo Erba), 1,4-dioxane (99.8%, Carlo Erba), tetrahydrofuran (THF, >99.8%, Carlo Erba), diisopropyl ether (99%, Carlo Erba), *N,N*-dimethylformamide (DMF, 99.8%, Carlo Erba), hexane (99.9%, Honeywell), 8-hydroxyquinoline (8HQ, >99%, TCI chemical), 2-mercaptoethanol (99%, Acros Organics), triethylamine (Et_3N , 99.5%, Carlo Erba), di-sodium tetraborate decahydrate (Quality Reagent Chemical, 99.5%), tetrabutylammonium bromide (99%, Acros Organics), 1,1'-azobis (cyclohexanecarbonitrile) (ABCN, 98%, Sigma-Aldrich), nicotinic acid (>99%, TCI chemical), 1H-Benzotriazole (99%, Acros Organics), sodium phosphate (98%, Carlo Erba), sodium hydroxide (98%, Carlo Erba), dodecyl sulfate (SDS, 99%, Acros Organics), orthophosphoric acid (85%, Carlo Erba), chloroform-D (99.8%, Cambridge Isotope Laboratories) was used without further purification.

S1.2. Synthesis of 8-quinolinyl-sulfide-ethyl methacrylate (HQSEMA)

QAOH (14.5 g, 52 mmol) was dissolved in 50 mL of DCM and stirred at 0 °C in an ice-bath. Subsequently, a solution of methacryloyl chloride (8.17 mg, 79 mol) in 15 ml DCM in the present of Et_3N (8.42 mg, 83 mmol) was added dropwise to the reaction mixture kept under nitrogen. The reaction was stirred for 15 h at 0 °C in an ice-bath. The product was first extracted with cold deionized water (4x100 mL), with cold $NaHCO_3$ solution (2x100 mL), and with cold saturated NaCl (3x100 mL). The product was dried over $NaSO_4$, filtered, and evaporated with a rotary evaporator. The purification of product was performed by column chromatography on silica gel with a

mixture of hexane:EtOAc (2:1, v:v) to provide 1.5 g (10% yield) of a yellowish liquid (Figure S1). ^{1}H NMR spectroscopy (600 MHz, $CDCl_3$): δ = 1.95 (s, 3H, CH_3), 2.92 (t, J=7.0 Hz, 2H, CH_2), 3.08 (t, J=7.0 Hz, 2H, CH_2), 3.13 (t, J=7.15 Hz, 2H, CH_2), 4.37 (t, J=7.1 Hz, 2H, CH_2), 5.57 (s, 1H, CH_2), 6.13 (s, 1H, CH_2), 6.09 (s, 2H, CH_2), 7.43 (m, J=4.1 Hz, 1H, Ar), 7.46 (d, J=7.3 Hz, 1H, Ar), 7.53 (t, J=8.1 Hz, 1H, Ar), 7.72 (d, J=9.2 Hz, 1H, Ar), 8.18 (d, J=8.8 Hz, 1H, Ar), 8.91 (d, J=3.1 Hz, 1H, Ar). HRMS: calcd for $C_{18}H_{19}NO_4$ 346.1108 $[M+H]^+$, found 346.1151.

S1.3. Synthesis of 4-hydroxybutyl methacrylate (HBMA)

4-(vinyloxy)butyl methacrylate (VBMA, 15 g, 81.4 mmol) was dissolved in a mixture of 350 mL THF and 30 mL water. Then, 300 µL TFA was added to the reaction mixture which was stirred for 48 h at 25 °C. Finally, a solution of 500 mg of $NaHCO_3$ in 10 mL deionized water was added to the mixture. The solvents were partially removed in a rotary evaporator. Then, chloroform and 20 g of $NaSO_4$ were sequentially added. The mixture was filtrated and then chloroform was removed in a rotary to afford 4-hydroxybutyl methacrylate (HBMA) with a yield of 86% (Figure S2). ^{1}H NMR spectroscopy (600 MHz, $CDCl_3$): δ = 1.63 (m, J=7.5 Hz, 2H, CH_3), 1.75 (m, J=7.3 Hz, 2H, CH_2), 1.92 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 4.16 (s, 2H, CH_2), 5.53 (s, 1H, CH_2), 6.07 (s, 1H, CH_2),

S1.4. Synthesis of 4-(nicotinoyloxy) butyl methacrylate (NIBMA)

Nicotinoyl chloride hydrochloride (14 g, 78.6 mmol) was dissolved in 250 mL dry DCM. The mixture was cooled in ice-bath under nitrogen atmosphere. Then, a solution of HBMA (10 g, 63.3 mmol) and Et_3N (27 g, 267 mmol) in 100 mL dry DCM was added dropwise for 2 h to the solution of nicotinoyl chloride hydrochloride in DCM cooled by an ice bath. Afterwards, the reaction was continued for 12 h at room temperature. Then, the mixture was added to 250 mL deionized water containing crushed ice. The aqueous phase was removed with a separatory funnel and the organic phase was extracted two more times with cold deionized water, and one time with a cold solution of $NaHCO_3$ (5 g) and NaCl (10 g) in 100 mL of deionized water. Finally, the organic phase was dried over $MgSO_4$ and solvent was removed. The product was purified in a silica-gel column chromatography by washing first with EtOAc:hexane (1:5, v:v) to remove unreacted HBMA and then with EtOAc:hexane (2:1, v:v) to obtain NIBMA in 80% yield (Figure S3). ^{1}H NMR spectroscopy

(600 MHz, $CDCl_3$): δ = 1.86 (m, J=5.87, 2H, CH_3), 1.93 (d, J=5.3 Hz, 3H, CH_3), 4.22 (t, J=6.0 Hz, 2H, CH_2), 4.40 (t, J=6.3 Hz, 2H, CH_2), 5.54 (m, J=2.3 Hz, 1H, CH_2), 6.09 (d, J=4.0 Hz, 1H, CH_2), 7.38 (m, J=4.0 Hz, 1H, Ar), 8.27 (s, 1H, Ar), 8.76 (s, 1H, Ar), 9.56 (d, J=4.0 Hz, 1H, Ar). HRMS: calcd for $C_{14}H_{17}NO_4$ 346.2970$[M+H]^+$, found 264.1252.

S1.5. Synthesis of P(BMA-*co*- BEBMA-*co*-HQSEMA) (BTA-8HQ polymer)

BMA (1648 mg, 11.59 mmol), BEBMA (354, 1.159 mmol), HQSEMA (400 mg, 1.159 mmol), and ABCN (120 mg, 0.5 mmol) were dissolved in anhydrous DMF (15 mL). The solution was stirred and bubbled with nitrogen for 10 min and then stirred for 7 h in an oil bath at 85 °C under nitrogen atmosphere. Afterwards, the solution was precipitated in 200 mL of a 4:1 (v:v) hexane:diisopropyl ether mixture. The product was purified by three times redissolution/precipitation in chloroform and hexane. The final product was dried in vacuum to provide 1.9 g (79% yield) of P(BMA-*co*-HQSEMA-*co*-BEBMA). The proton signal of methylene in -OC**H_2**CH_2 of BMA, HQSEMA, and BEBMA units of copolymer in $CDCl_3$ (Figure S4) was detected at δ = 3.93 and 4.12 ppm and the signals of methylene in -OC**H_2**Ar of BEBMA unit, aromatic protons in benzotriazole, and aromatic protons in 8HQ appeared at δ = 6.05 and 6.25 ppm, δ = 7.38, 7.48, 7.78, 7.98, and 8.06 ppm, δ = 7.53, 7.72, 8.18, and 8.91 ppm, respectively. The composition of the copolymers was calculated from integral areas of the proton signals at δ = 3.93 and 4.12 ppm for all monomer, δ = 8.91 ppm for HQSEMA, and δ = 6.05 and 6.25 ppm for BEBMA. The amount of conjugated BTA and 8HQ in BTA-8HQ polymer were 5.9 wt% and 5.2 wt%, respectively. The total monomer conversion for P(BMA-*co*-BEBMA-*co*-HQSEMA) calculated from ^{1}H-NMR spectroscopy measurements was 91%. The apparent number-average molecular weight (M_n) and the molecular weight distribution (MWD) were 30,000 g mol^{-1} and 2.8, respectively.

S1.6. Synthesis of P(BMA-*co*-BEBMA-*co*-NIBMA-*co*-HQSEMA) (BTA-NA-8HQ polymer)

BMA (1648 mg, 11.59 mmol), BEBMA (354, 1.159 mmol), NIBMA (306 mg, 1.159 mmol), HQSEMA (400 mg, 1.159 mmol), and ABCN (134 mg, 0.6 mmol) were dissolved in anhydrous DMF (15 mL). The mixture solution was stirred and bubbled with nitrogen for 10 min and then stirred for 7 h in an oil bath at 85 °C under nitrogen atmosphere. Then, the solution was precipitated in 200 mL of

a 5:1 (v:v) mixture of hexane: diisopropyl ether. The product was purified by three times redissolution/precipitation in chloroform and hexane. The final product was dried in vacuum to provide 2.4 g (89% yield) of P(BMA-*co*-BEBMA-*co*-NIBMA-*co*-HQSEMA). The proton signal of methylene in -OC**H$_2$**CH$_2$ of BMA, HQSEMA, BEBMA, and NIBMA units of copolymer in $CDCl_3$ (Figure S5) was detected at δ = 3.93 and 4.12 ppm and the signals of methylene in -OC**H$_2$**Ar of BEBMA unit, aromatic protons in benzotriazole, aromatic protons in 8HQ, and aromatic protons of NA appeared at δ = 6.05 and 6.25 ppm, δ = 7.38, 7.48, 7.78, 7.98, and 8.06 ppm, δ = 7.53, 7.72, 8.18, and 8.91 ppm, δ = 8.27, 8.76, and 9.56 ppm, respectively. The composition of the copolymers was calculated from integral areas of the proton signals at δ = 3.93 and 4.12 ppm for all monomer, δ = 8.91 ppm for HQSEMA, δ = 6.05 and 6.25 ppm for BEBMA, and δ = 9.56 ppm for NIBMA. The amount of conjugated BTA, NA, and 8HQ in the polymer were 5 wt%, 4.6 wt%, and 4.8 wt%, respectively. The total monomer conversion for P(BMA-*co*-BEBMA-*co*-NIBMA-*co*-HQSEMA) calculated from ^{1}H-NMR spectroscopy measurements was 95%. The apparent number-average molecular weight (M_n) and the molecular weight distribution (MWD) were 34,500 g mol^{-1} and 3.1, respectively.

S1.7. Nanoparticles formation by the miniemulsion-solvent evaporation process

200 mg of copolymer dissolved in 3.3 g DCM was added to 12 mL of a 0.02 M phosphate buffer at pH 7 solution containing SDS (18 mg). The mixture was stirred at 1000 rpm at room temperature for 20 min. Then, a miniemulsion was prepared by ultrasonication (Branson Sonifier SFX550) with 3/4 in. tip at 50% amplitude pulse mode for 90 s (0.25s pulse, 1s pause) in an ice bath. DCM in the dispersion was removed with a rotary evaporator at 30 °C to obtain a nanoparticles dispersion.

S1.8. Release of payloads from the nanoparticles

To study the release from the dispersions, 6 mL of nanoparticle dispersions (containing 100 mg polymer) were mixed with 114 mL of silica-gel column chromatograph a 0.05 M phosphate buffer solution containing 85.5 mg SDS at pH 3.0, 5.0, or 7.0. At different time intervals, 10 mL of the mixture was taken out, placed in liquid nitrogen, and freeze-dried. Then, 14 mL cold deionized

water was added to the freeze-dried sample that was shaken to extract salts and surfactant. The sample was then centrifuged at 9000 rpm for 5 min at 4 °C. The remaining solid was dried and dissolved in $CDCl_3$ to measure the amount of the remaining payloads by ^{1}H-NMR spectroscopy.

S1.9. Preparation of polymer coatings

Cold rolled steel substrates (99.295wt% Fe, 0.5wt% Mn, 0.12wt% C, 0.04wt% P, and 0.045wt% S) with 1 mm thickness (CRS: SPCC) were used for corrosion measurements. The substrates were cut into 20×20 mm squares and polished under water with SiC abrasive papers (80, 180, 360 and 600 grid grades). The steel samples were cleaned with deionized water and ultrasonicated twice in methanol (25 mL) for 10 min. Then, the samples were dried in desiccators for 1 h. The substrates were masked by a polyester film tape (3M) to leave an uncover area of steel with a dimension of 10×10 mm. 10 mg polymer dissolved in a mixture of chloroform (50 µL) and toluene (50 µL) was drop-cast on steel substrates. The coated substrates were dried at room temperature for 2 h and kept overnight in a desiccator.

S1.10. Analytical tools

^{1}H and ^{13}C NMR spectra were obtained on a Bruker 600 MHz NMR spectrometer at room temperature in $CDCl_3$. Molecular weights of low molecular weight compounds were determined by LC-Quadrupole-Time-of-Flight Tandem Mass Spectrometry (MS, model Compact QTOF, Bruker). The molecular weights of the polymers were determined by gel permeation chromatography (GPC, model Viscotek TDAmax, Malvern). The polymers were dissolved in THF with a concentration of 3 mg/ml and then the polymer solution was filtrated through a PTFE membrane filter (0.45 mm pore size). Three single-pore GPC/SEC columns (6, 7 and 10 µm particle size, linear M) heated at 35 °C with a flow rate of 1 ml/min and a RI-detector were used. For calibration, polystyrene from PSS (Mainz) with different molecular weight was used. The particle size was measured by dynamic light scattering (DLS, model NanoPlus-3, Micromeritics) with a laser wavelength of 660 nm and a detection angle at 165°. The thickness of the coatings was determined with a profilometer (DektakXT, Bruker). The electrochemical measurements were performed with a potentiostat (Autolab PGSTAT302N, Metrohm Siam Ltd.). In a standard

three-electrode setup, steel samples were used as working electrode, Ag/AgCl in 3 M KCl was the reference electrode, while a platinum counter electrode was added. The measurements were performed at room temperature (25 ± 2 °C) in a 0.1 M HCl aqueous solution. Polarization curves were recorded after 30 min equilibrium in an open circuit potential (OCP) configuration. Potential was scanned from -0.75 V to 0.75 V with a scan rate of 1 mV s^{-1}. Tafel plots were extrapolated to determine the corrosion potential E_{corr}, the corrosion current density j_{corr}, the polarization resistance R_p, and the corrosion rate (CR) using the Nova version 2.0 software. Thermogravimetric analysis was performed under nitrogen atmosphere with a heating rate of 10 °C min^{-1} from 25 to 700 °C with a LINSEIS STA PT 1600 thermogravimetric analyzer.

S2 Supplementary Figures

NMR spectra

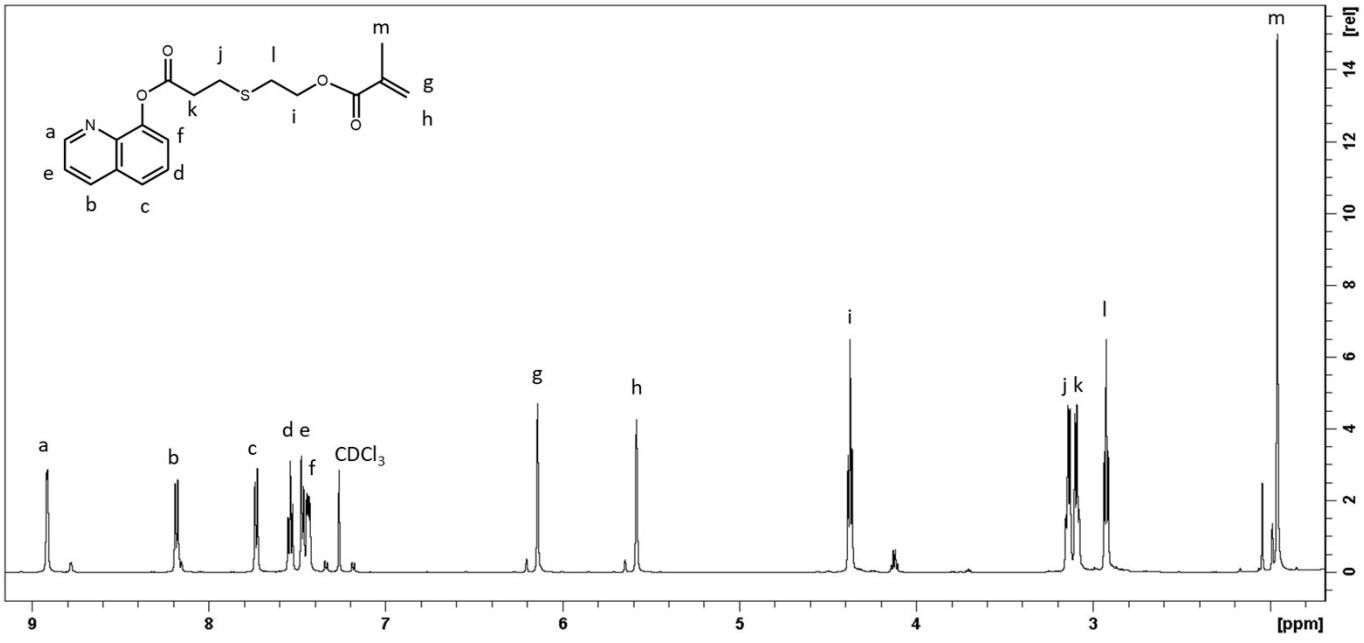


Figure S1. ^{1}H-NMR spectrum of HQSEMA in $CDCl_3$.

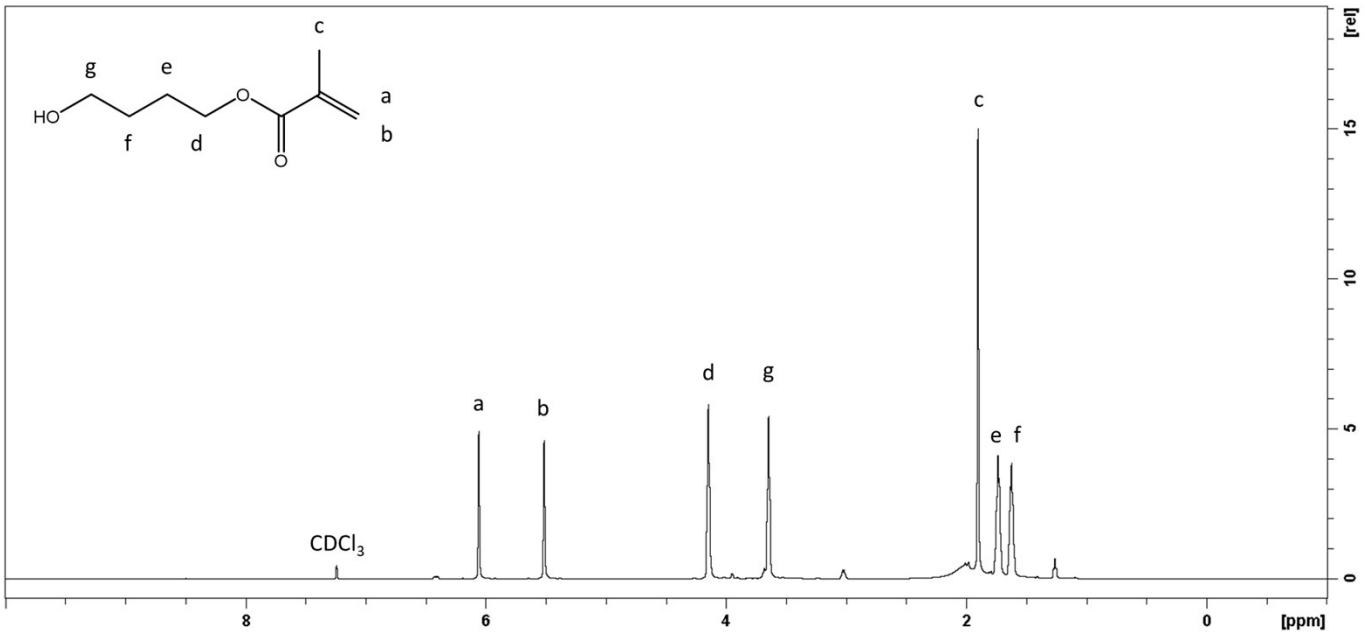


Figure S2. ^{1}H-NMR spectrum of HBMA in $CDCl_3$.

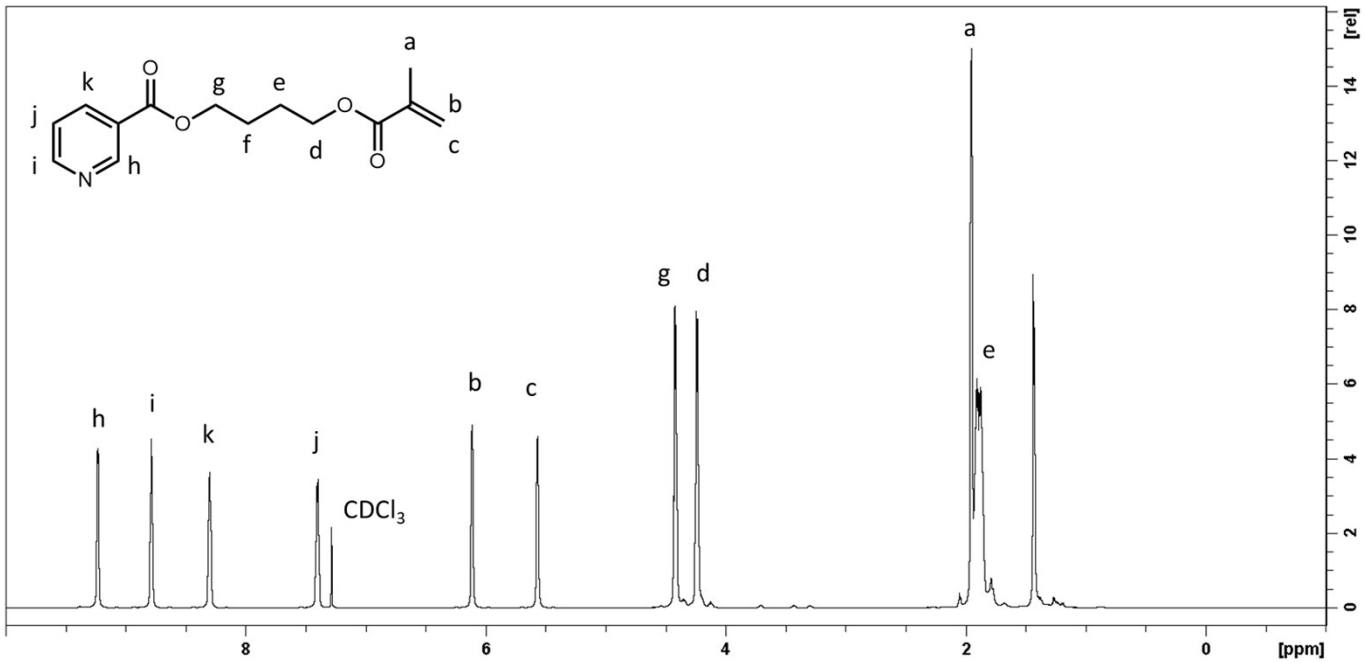


Figure S3. ^{1}H-NMR spectrum of NIBMA in $CDCl_3$.

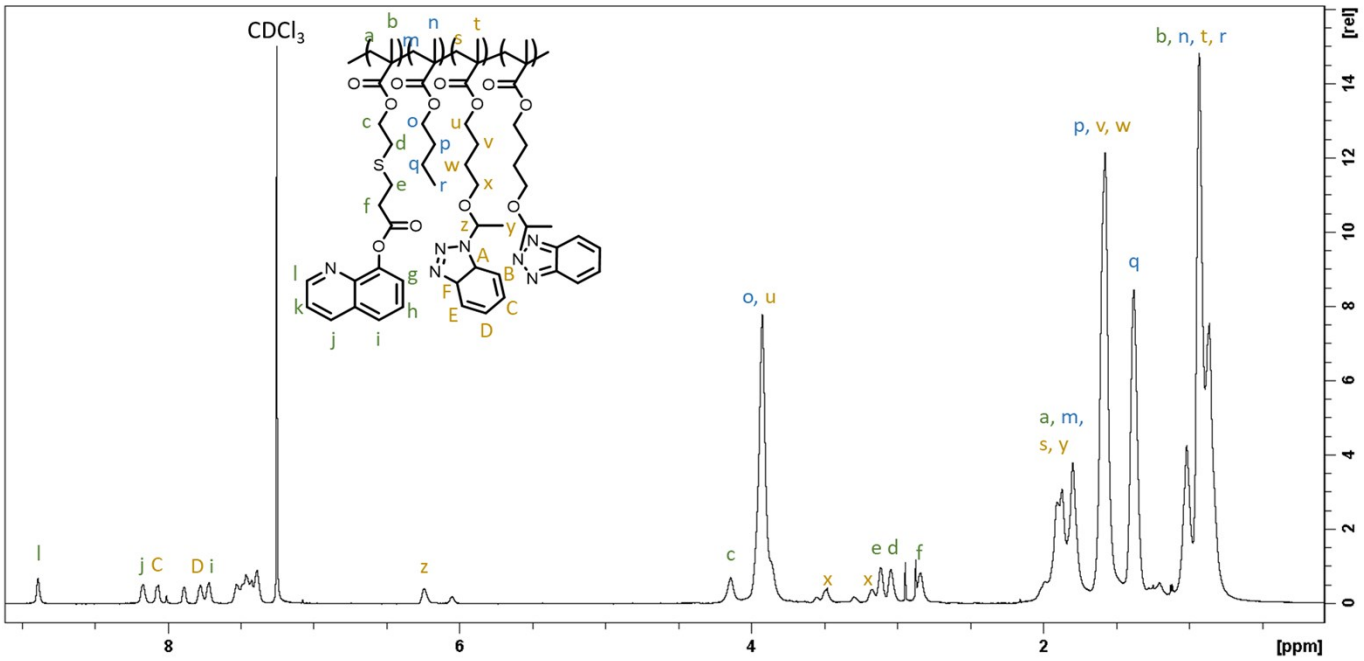


Figure S4. ^{1}H-NMR spectrum of poly[*n*-butyl methacrylate)$_{0.75}$-*co*-(4-(1-(benzotriazole-*N*-yl)ethoxy) butyl methacrylate)$_{0.13}$-*co*-(8-quinolinyl-sulfide-ethyl methacrylate)$_{0.12}$] (BTA-8HQ polymer) in $CDCl_3$.

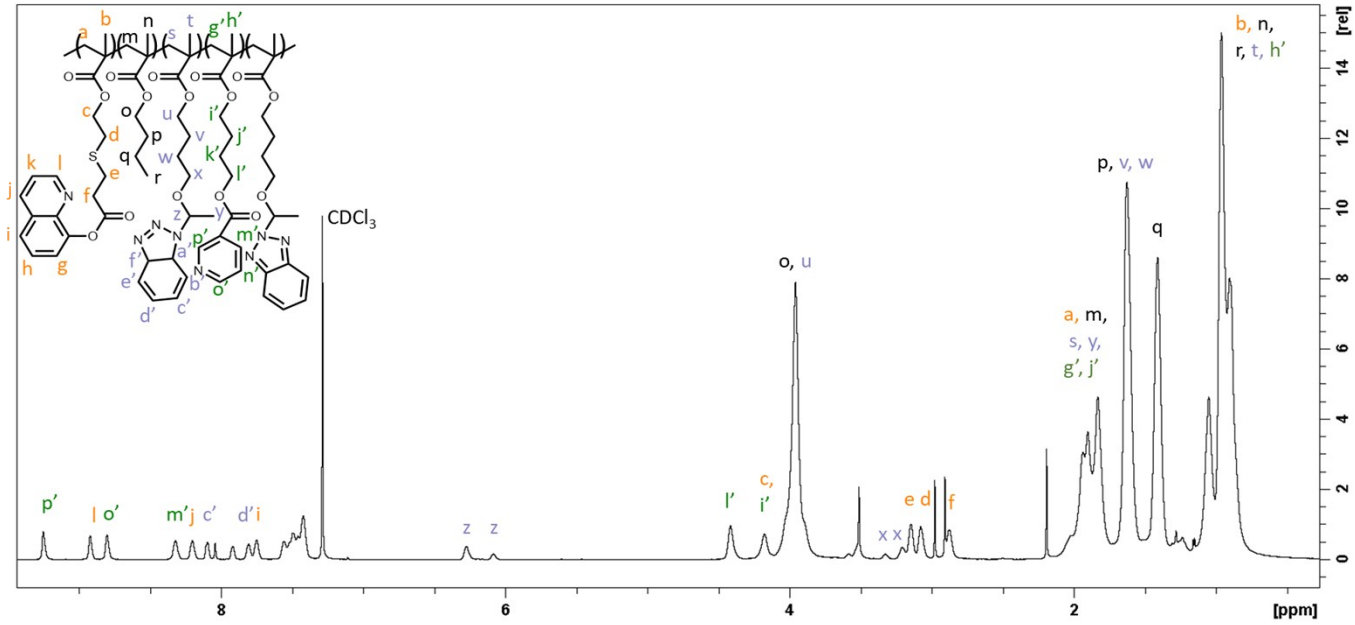


Figure S5. ^{1}H-NMR spectrum of poly[*n*-butyl methacrylate)$_{0.67}$-*co*-(4-(1-(benzotriazole-*N*-yl)ethoxy) butyl methacrylate)$_{0.12}$-*co*-(8-quinolinyl-sulfide-ethyl methacrylate)$_{0.11}$-*co*-(4-(nicotinoyloxy) butyl methacrylate)$_{0.10}$] (BTA-NA-8HQ polymer) in $CDCl_3$.

TGA thermograms

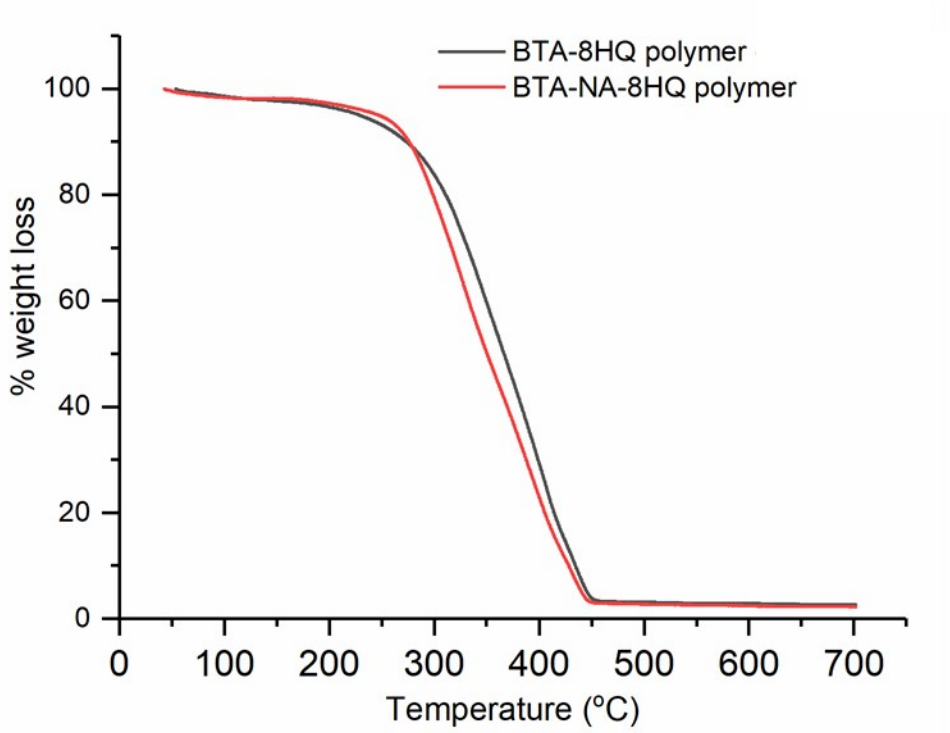


Figure S6. Thermograms displaying the thermal stability of poly[*n*-butyl methacrylate)$_{0.75}$-*co*-(4-(1-(benzotriazole-*N*-yl)ethoxy) butyl methacrylate)$_{0.13}$-*co*-(8-quinolinyl-sulfide-ethyl methacrylate)$_{0.12}$] (BTA-8HQ polymer), poly[*n*-butyl methacrylate)$_{0.67}$-*co*-(4-(1-(benzotriazole-*N*-yl)ethoxy) butyl methacrylate)$_{0.12}$-*co*-(8-quinolinyl-sulfide-ethyl methacrylate)$_{0.11}$-*co*-(4-(nicotinoyloxy) butyl methacrylate)$_{0.10}$] (BTA-NA-8HQ polymer)

Anticorrosion performance

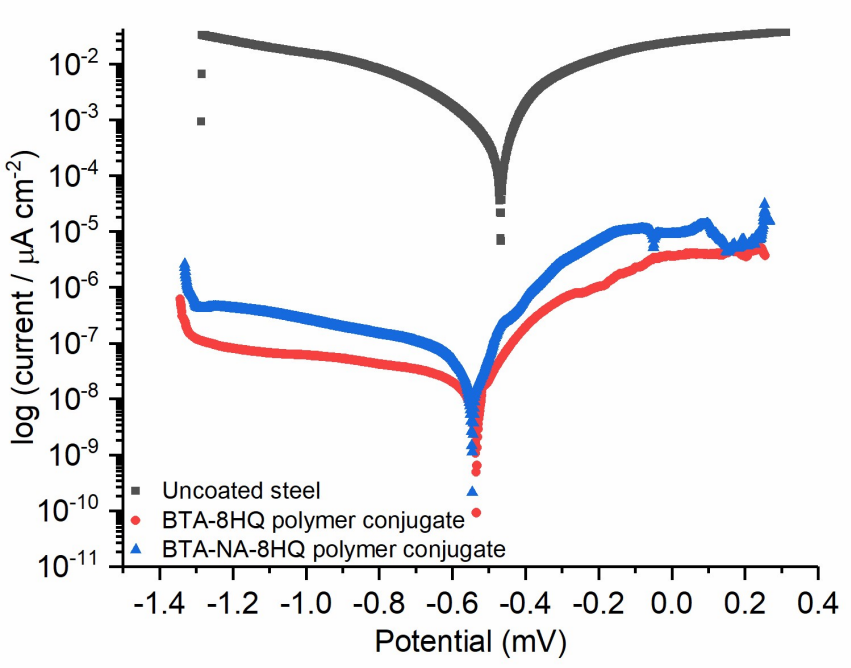


Figure S7. Tafel plots of uncoated steel and steel coated with BTA-8HQ polymer and BTA-NA-8HQ polymer) in 0.1 M HCl aqueous solution.

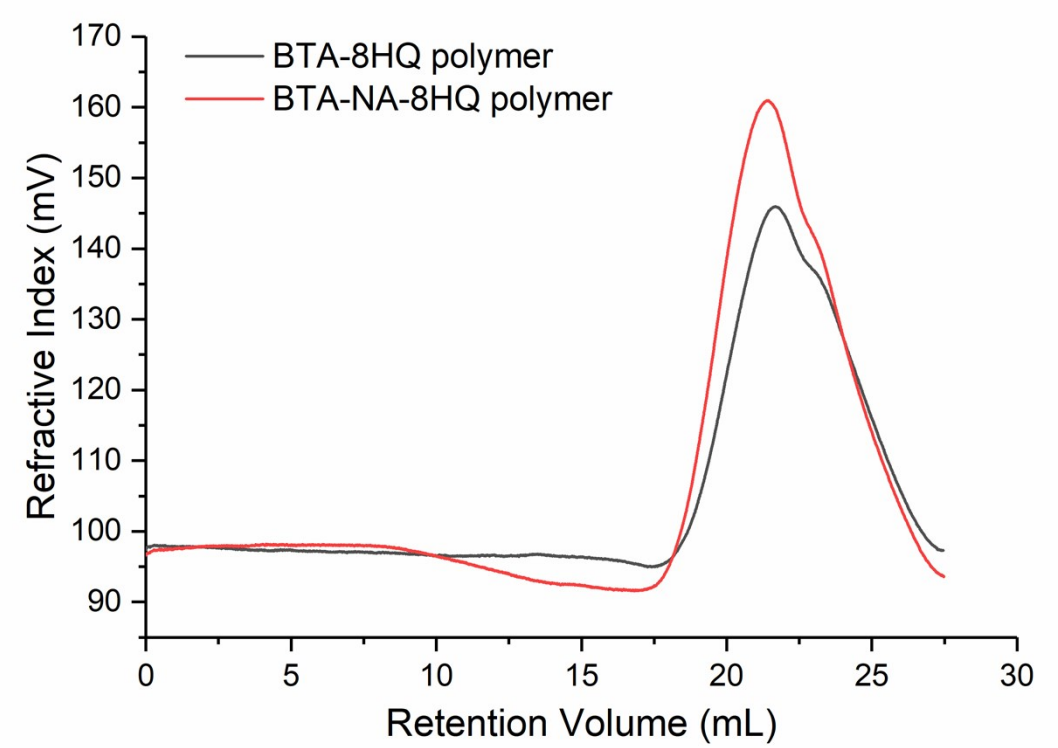


Figure S8. GPC chromatograms of BTA-8HQ and BTA-NA-8HQ polymer.

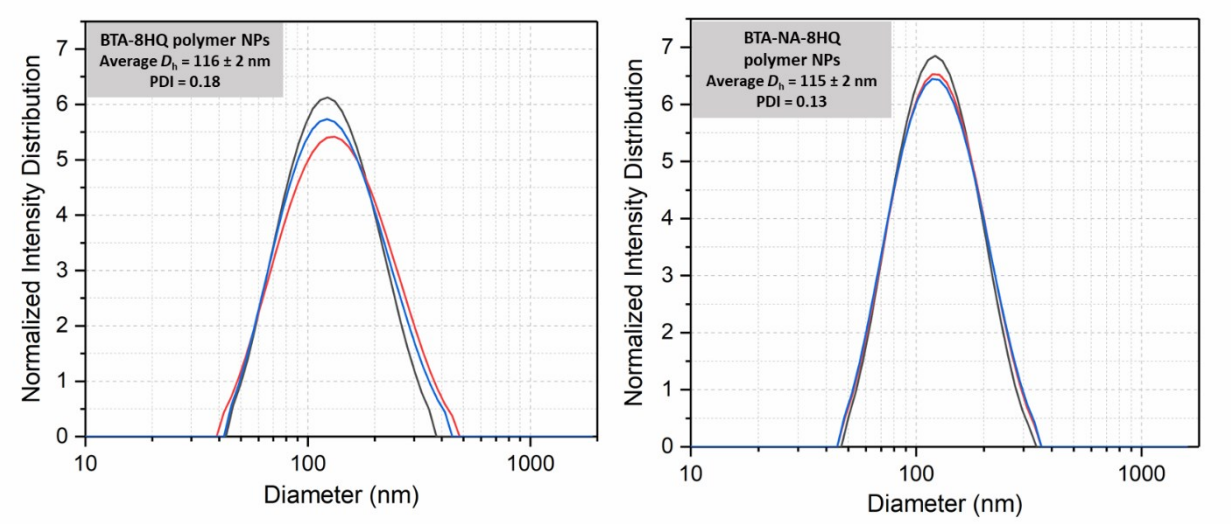
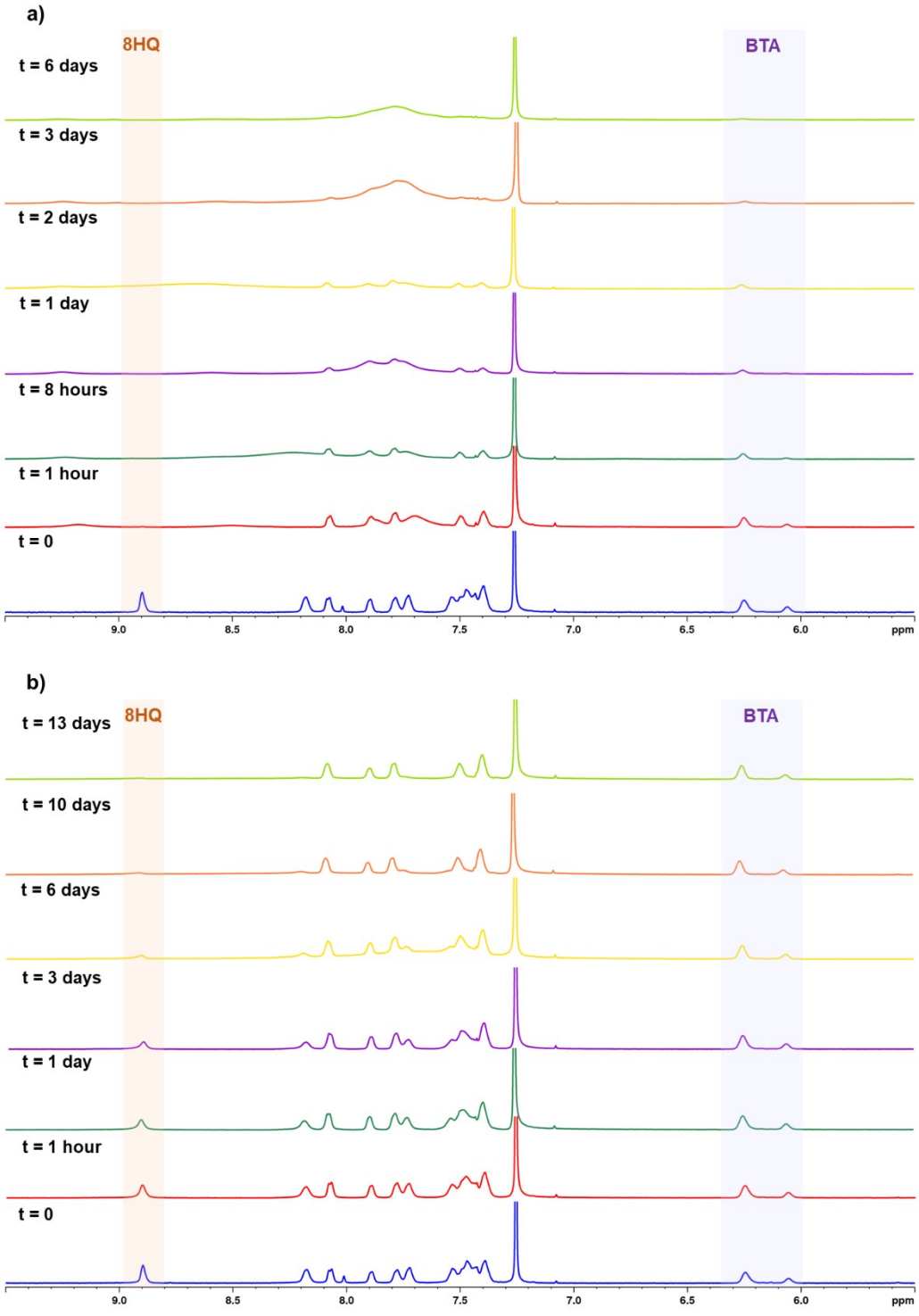


Figure S9. DLS size distribution of BTA-8HQ and BTA-NA-8HQ polymer nanoparticles in water.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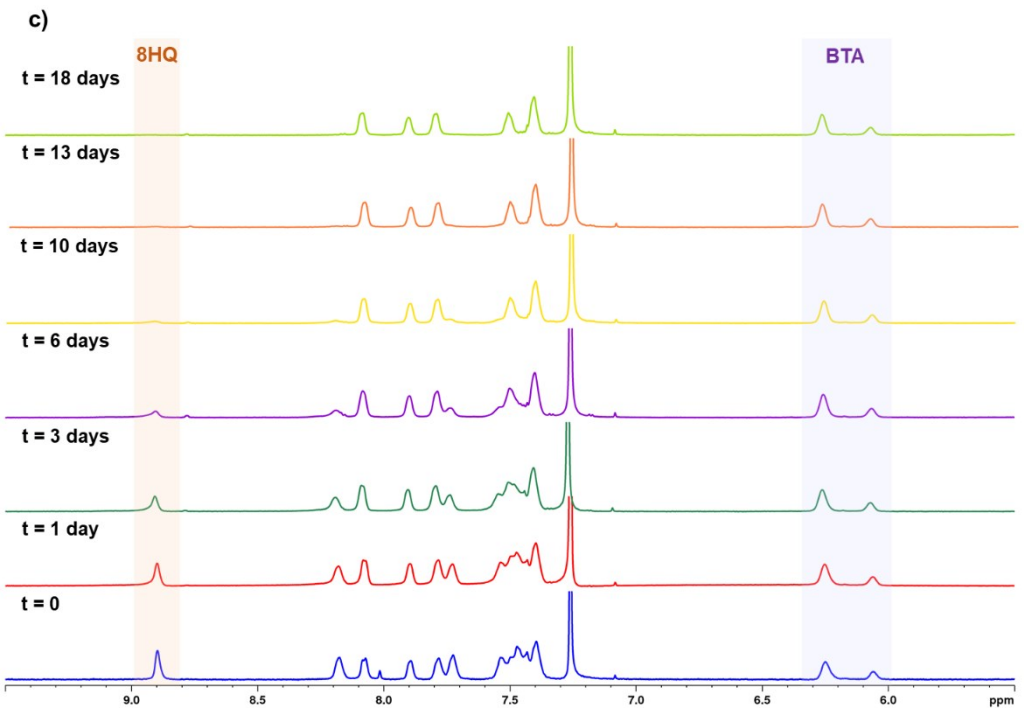
8HQ
BTA
t = 6 days
t = 3 days
t = 2 days
t = 1 day
t = 8 hours
t = 1 hour
t = 0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
ppm
b)
8HQ
BTA
t = 13 days
t = 10 days
t = 6 days
t = 3 days
t = 1 day
t = 1 hour
t = 0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
ppm


c)
8HQ
BTA
t = 18 days
t = 13 days
t = 10 days
t = 6 days
t = 3 days
t = 1 day
t = 0
9.0
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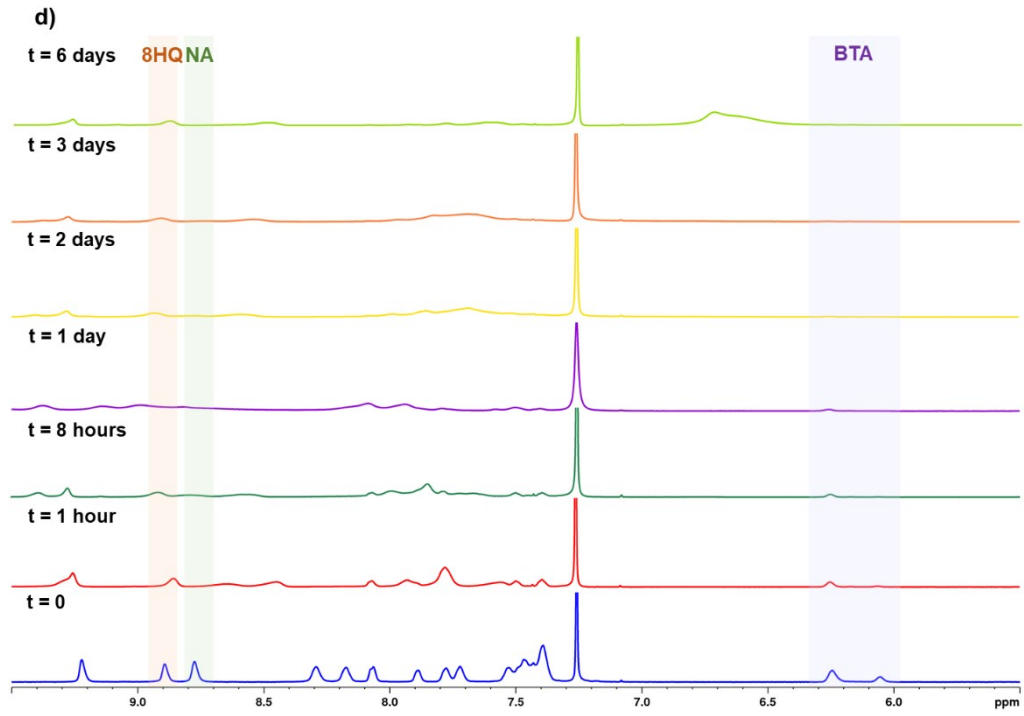
8.0
7.5
7.0
6.5
6.0
ppm


d)
t = 6 days
8HQNA
BTA
t = 3 days
t = 2 days
t = 1 day
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8.0
7.5
7.0
6.5
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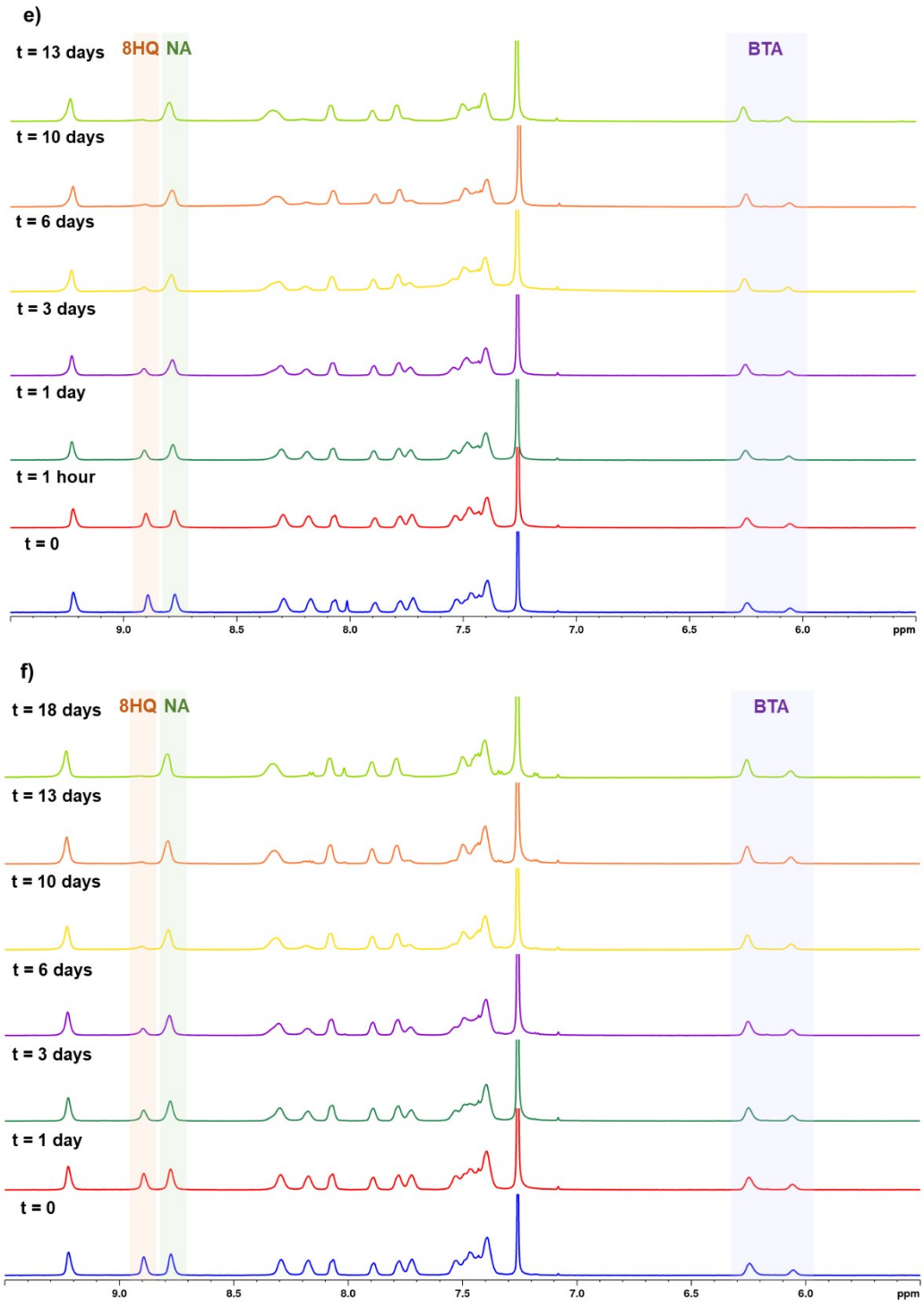

Figure S10. ^{1}H NMR spectra of BTA-8HQ (a-c) or BTA-NA-8HQ (d-f) polymer nanoparticles dissolved in $CDCl_3$ after the release experiments in buffer solutions pH 3.0 (a, d), pH 5.0 (b, e), and pH 7.0 (c, f) at different time intervals.

References

S1. V. Dhanapal and K. Subramanian, *Carbohydr. Polym.,* 2015, **117**, 123-132.

S2. N. Dararatana, F. Seidi and D. Crespy, *ACS Appl. Mater. Interfaces,* 2018, **10**, 20876-20883.

S3. M. Keenan, M. J. Abbott, P. W. Alexander, T. Armstrong, W. M. Best, B. Berven, A. Botero, J. H. Chaplin, S. A. Charman and E. Chatelain, *J. Med. Chem.,* 2012**, 55**, 4189-4204.

S4. F. Seidi, V. Druet, N. Huynh, T. Phakkeeree and D. Crespy, *Chem. Commun.*, 2018, **54**, 13730-13733.